REMARKS

This is a full and timely response to the Office Action mailed October 17, 2003.

Claims 1-3 and 6 were amended. Support for the claim amendments can be found throughout the specification and the original claims, see for example, page 5, lines 6-11. By this Amendment, Applicant believes that all pending claims are in condition for allowance. Reexamination and reconsideration in light of the above amendments and the following remarks is respectfully requested.

Rejection under 35 U.S.C. § 112

Claims 1-6 are rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Applicant respectfully traverses this rejection.

However, even though Applicant disagrees with the Examiner in this regard, in the interest of expediting prosecution, Applicant has effected minor clarifying amendments to the claims to overcome this rejection. Specifically, Applicant has amended claim 1 to clarify that the claimed object of analysis *(1) consists of nucleic acid or a nucleic acid fragment having a base sequence and (2) includes a plurality of inspected sites in the base sequence to be subjected to inspection of mutation.* Applicant believes that such an amendment clarifies that a plurality of differently label oligonucleotides are used to detect multiple mutations in a single nucleic acid sequence.

Applicant has also amended claim 6 to a single PCR "cycle" in accordance with the Examiner's suggestion. No new matter has been added since the term "step", as presented in the claims and on page 5, lines 6-11, of the specification, is used synonymously with the term "cycle". Such an understanding would be clearly recognized by one skilled in the art.

In response to item 6 on page 3 of the Action, Applicant has further reviewed claims 1-6 and effected some additional claim amendments to put the claims in their best form under U.S. practice. Applicant believes that no other changes should be necessary since the same claims have been examined three times by the Patent Office.

If, however, there are any additional changes which are needed, the Examiner is kindly requested to provide specific description of such changes in subsequent Actions.

Rejection under 35 U.S.C. § 103

Claims 1-6 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gjerde et al. (U.S. Patent 6,210,885). Applicant respectfully traverses this rejection.

Gjerde et al. teach a method for the detection of a mutation in a sample double stranded DNA fragment. The method includes (a) covalently attaching a chemical tag to the sample DNA fragment or to a corresponding wild type fragment to form a tagged polynucleotide, (b) hybridizing the sample DNA fragment with the corresponding wild type DNA fragment to form a mixture of homoduplexes and heteroduplexes if a mutation is present in the sample DNA fragment, (c) applying the product of step (b) to a separation medium having a non-polar surface, (d) eluting the mixture with a mobile phase containing a counterion agent and an organic solvent where the eluting is carried out under conditions effective to at least partially denature the heteroduplexes and where the eluting results in the separation of the heteroduplexes from the homoduplexes, and (e) detecting the tagged polynucleotide. Gjerde et al. also teach using fluorescent dyes as a label, increasing melting temperature to detect mutation, and detecting mutation through the separation of peaks.

However, as the Examiner correctly notes on the bottom of page 4 of the Action, Gjerde et al. fail to specifically teach the use of a plurality of differently labeled oligonucleotides of varying types to detect a plurality of mutation sites on a single nucleic acid fragment.

The Examiner addresses this deficiency by arguing that the plurality of differently label primers taught in Gjerde et al. (for amplifying different regions of the DNA template, see column 28, lines 9-47) can also serve as oligonucleotides probes to detect a plurality of mutation sites on a single DNA fragment. The Examiner argues that one skilled in the art would be motivate to apply this method of Gjerde et al. since Gjerde et al. also disclose detecting "multiplex" mutations in a DNA sample via DMIPC.

Applicant, however, disagrees with the Examiner in this regard. The term "multiplex", as described in Gjerde et al., involve detecting each DNA sample independently from a plurality of DNA samples. In column 28, lines 9-24, Gjerde et al. states

> In an important aspect of the invention, ***mixtures of dsDNA*** tagged with different fluorescent dyes which are "uniquely detectable" ***from each other***, can be used in "multiplex" applications to detect ***each component of a mixture***

> ***independently of the other components of the mixture***. The term "multiplex" is defined herein to mean the selective and simultaneous detection of each desired component of a mixture in the presence of all the other components of the mixture. The term "uniquely detectable" as used herein, means that the fluorescent emission (in the case of fluorophores) or absorbance (in the case of tags absorbing in the uv-vis spectrum) wavelength of each dye in a mixture is sufficiently distinct from every other dye so that ***every DNA fragment which is tagged with a different dye can be distinguished from any other tagged DNA fragment in the mixture***.

Also, in column 28, lines 27-39, Gjerde et al., only describe how four expected PCR products can be ***monitored simultaneously*** by chromatographing the mixture on MIPC column (*using four differently labeled primers*) and monitoring the separation at any of the wavelengths corresponding to the dyes used.

In other words, in reviewing the above passages (cited by the Examiner) and Gjerde et al. as a whole, it is clear that Gjerde et al. fail to describe using the four differently labeled primers to detect ***a plurality of mutation sites on a single DNA fragment***. Gjerde et al. only teach the analysis of a single mutation and the simultaneous monitoring of a plurality of DNA fragments.

For example, in Examples 3 and 4, columns 34 and 35, of Gjerde et al., portions of the 6-FAM and JOE tagged DYS 81 "A" allele samples described in Example 2 were analyzed in a multiplex fashion (FIG. 16 using fluorescence detection (Hitachi Model L-7480 fluorescence detector). However, ***only a single mutation*** site at position 168 on a 209 base pair fragment (from the human Y chromosome locus DYS271) was analyzed. Other multiplex examples can also be found in column 31, lines 42-50, in which Gjerde et al. describe using different fluorescent tags to monitor ***a plurality of DNA fragments***.

Applicant was unable to find, based on his review of Gjerde et al., any teaching or suggestion which reads on or render obvious the claimed limitation "*said object of analysis . . . (2) including a plurality of inspected sites in the base sequence to be subjected to inspection of mutation*" In fact, in the whole reference of Gjerde et al., a DNA sample having a plurality of mutations was never disclosed or discussed.

As the Examiner already knows, to establish a *prima facie* case of obviousness, the cited reference either alone or in combination, must teach or suggest all the limitations of the claims. The Examiner is not allowed under U.S. case law to insert teachings from the present

claims (i.e. "*said object of analysis . . . (2) including a plurality of inspected sites in the base sequence to be subjected to inspection of mutation*") into Gjerde et al. just because the reference teach a ***different*** "multiplex" application of detecting ***each component of a mixture independently of the other components of the mixture***. The Examiner's argument (beginning on the bottom of page 4 of the Action) that one skill in the art would have been motivated to apply the method of Gjerde et al. to detect a plurality of mutation sites on a single DNA fragment, uses the teachings of the present application as motivation to arrive at the present invention. As discussed above, Gjerde et al. do not at all teach using a plurality of differently labeled primers to detect multiple mutations on a single DNA fragment.

To construct a proper *prima facie* case of obviousness in this case, the Examiner must cite the specific teaching "*said object of analysis . . . (2) including a plurality of inspected sites in the base sequence to be subjected to inspection of mutation*" **in a prior art reference and not from the Applicant's disclosure**.

Thus, since Gjerde et al. fails to teach or suggest a specific limitation of the claims, the obviousness rejection under 35 U. S. C. § 103 cannot be sustained and should be withdrawn.

CONCLUSION

For the foregoing reasons, all the claims now pending in the present application are believed to be clearly patentable over the outstanding rejections. Accordingly, favorable reconsideration of the claims in light of the above remarks is courteously solicited. If the Examiner has any comments or suggestions that could place this application in even better form, the Examiner is requested to telephone the undersigned attorney at the below-listed number.

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Respectfully submitted,

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